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| EXAMINER |
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STOICA, ELLY GERALD

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| ART UNIT | PAPER NUMBER |
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1647

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09/15/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/593,518

Applicant(s)

NISHIKAWA ET AL.

Examiner

ELLY-GERALD STOICA

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 June 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-38 is/are pending in the application.
- 4a) Of the above claim(s) 1-7 and 27-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-893)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of claims 18-26 in the reply filed on 06/25/2008 is acknowledged.

Status of the claims

2. Claims 1-38 are pending. Claims 1-17 and 27-38 are withdrawn as being drawn to non-elected subject matter. Claims 18-26 are currently examined.

Claim Objections

3. Claim 18 is objected to because of the following informalities: depending form a non-elected claim. Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 18-23 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, the protein claimed of SEQ ID NO: 2 is a product of nature and thus precluded from obtaining a patent. Amendment of the claims to read "isolated", "purified" or such would be remedial.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 18-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the independent claim 18 is indefinite because the metes and bounds of such recitations as: "fragment thereof", "variant" (absent any structure or no function required, no upper limit on changes), "hybridizing under stringent conditions" (again, with no structure or function required) cannot be determined. The claim 19 is indefinite because the variant recited in subheading c) does not provide an upper limit on mutations. Also, the recitation "Containing", as used in claim 19, for example, has no well defined legal meaning, and could mean "consisting of" or "comprising". In the interest of compact prosecution, it is being given its broadest reasonable interpretation, "comprising".

7. In claim 20 the recitation "a" nucleotide sequence set forth in SEQ ID NO: 1 is unclear since it may be interpreted as there might be more sequences of SEQ ID NO: 1. A recitation like "the nucleotide sequence..." would be remedial. In the same line of reasoning, the claim 21 is indefinite since it contains the recitation "an amino acid sequence set forth in SEQ ID NO: 2; using the definite article "the" would be remedial.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 18-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a protein having at least 70% identity with a protein of SEQ ID NO: 2 (or to a protein encoded by a polynucleotide having 70% identity with the polynucleotide of SEQ ID NO: 1), or encoded by a nucleic acid that hybridizes under "stringent conditions" to that of SEQ ID NO:1, or which has unlimited substitutions or alterations as compared to SEQ ID NO: 2 wherein the polypeptide has an activity selected from the group consisting of a vascular endothelial cell growth activity, activity in promoting transcription from c-fos promoter, activity in promoting transcription from VEGF promoter, and angiogenesis activity.

The specification provides the functional limitation of a peptide of the Invention as having at least one activity selected from vascular endothelial cell growth activity, activity in promoting transcription from c-fos promoter, activity in promoting transcription from VEGF promoter and angiogenesis activity (p. 10, lines 15-20). With respect to the structural limitations, the following is disclosed (p. 4, lines 10-24 and p.7, lines 10-23):

A) A polypeptide encoded by polynucleotide selected from the group consisting of:

(a) a polynucleotide containing a nucleotide sequence set forth in SEQ ID NO: 1 or a fragment thereof;

(b) a polynucleotide containing a sequence encoding an amino acid sequence set forth in SEQ ID NO:2 or a fragment thereof;

(c) a polynucleotide encoding a variant polypeptide wherein in a amino acid sequence set forth in SEQ ID NO:2, one or more amino acids thereof have at least one mutation selected from the group consisting of substitution, addition and deletion;

(d) a polynucleotide hybridizing under stringent conditions with any of the polynucleotides (a) to (c); and

(e) a polynucleotide consisting of a nucleotide sequence having at least 70% identity with any of the polynucleotides (a) to (c) or sequences complementary thereto.

B) A polypeptide selected from the group consisting of:

(a) a polypeptide containing an amino acid sequence encoded by a nucleotide sequence set forth in SEQ ID NO: 1 or a fragment thereof;

(b) a polypeptide containing an amino acid sequence set forth in SEQ ID NO: 2 or a fragment thereof;

(c) a variant polypeptide wherein in an amino acid sequence set forth in SEQ ID NO:2, one or more amino acids have at least one mutation selected from the group consisting of substitution, addition and deletion; and

(d) a polypeptide consisting of an amino acid sequence having at least 70% identity with an amino acid sequence of any one of the polypeptides (a) to (c).

The specification also describes a "fragment" as to a polypeptide or polynucleotide having a sequence length of from 1 to n-1 relative to a full-length polypeptide or polynucleotide (whose length is n). The length of a fragment can be changed depending on the object, and the lower limit of a polypeptide for example is a length of 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50 or more amino acids, and a length expressed by an integer not specifically enumerated herein (for example, or the like) can also be suitable as the lower limit. The lower limit of a polynucleotide is a length of 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100 or more nucleotides, and a length expressed by an integer not specifically enumerated herein can also be suitable as the lower limit (p. 15, lines 12-24). Thus, according to this description, even a single amino acid is envisioned as being encompassed by the claims.

The specification describes a "variant" as a substance derived from the original polypeptide or polynucleotide by partial modification. Such variants include, but are not limited to, substituted variants, added variants, deleted variants, truncated variants, allelic variants, and the like. Such variants include, but are not limited to, those having one or several substitutions, additions and/or deletions, or one or more substitutions, additions and/or deletions in their nucleic acid molecule or polypeptide standard. Alleles refer to genetic variants belonging to the same gene locus which are discriminated from each other. Accordingly, the term "allelic mutants" refers to those variants in the

relationship of alleles to a certain gene (p. 33, line 2-12). The substitution of amino acids means that the original peptide is substituted with one or more amino acids, for example, 1 to 10 amino acids. The addition of amino acids means that one or more amino acids, for example, 1 to 10 amino acids. The deletion of amino acids means that one or more amino acids, for example, 1 to 10 amino acids. The modification of amino acids includes, but is not limited to, amidation, carboxylation, sulfation, halogenation, truncation, lipidation, phosphorylation, alkylation, glycosylation, phosphorylation, hydroxylation, and acylation (for example, acetylation). The amino acids to be substituted or added may be naturally occurring amino acids or may be non-natural amino acids or amino acid analogs (p.36, lines 1-18).

Thus, the claims are drawn to a genus of proteins that is defined only by partial or no sequence identity or by undisclosed alterations which would not indicate which part of the molecule is to be conserved for the functionality of the protein.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polynucleotide species (SEQ ID NO: 1) and one polypeptide species (SEQ ID NO: 1) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments and with at least 70% identity with the protein of SEQ ID NO: 2

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (See *Vas-Cath* at page 1116).

With the exception of the SEQ ID NO:2 the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides or proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF’s were found to

be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the nucleic acid consisting of the sequence of SEQ ID NO: 1 or the polypeptide of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

10. Claims 18, 19 and 22-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide having the SEQ ID NO: 2 being encoded by a polynucleotide of SEQ ID NO: 1, or a fragment thereof that retains one or more of the activities recited in claim 19, for example, does not reasonably provide enablement for a protein having at least 70% identity with a protein of SEQ ID NO: 2 or unspecified mutants of it (or to a protein encoded by a polynucleotide having 70% identity with the polynucleotide of SEQ ID NO: 1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and

8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a protein having at least 70% identity with a protein of SEQ ID NO: 2 (or to a protein encoded by a polynucleotide having 70% identity with the polynucleotide of SEQ ID NO: 1), wherein the polypeptide has an activity selected from the group consisting of a vascular endothelial cell growth activity, activity in promoting transcription from c-fos promoter, activity in promoting transcription from VEGF promoter, and angiogenesis activity. Also claimed are pharmaceutical compositions containing the peptide for modulation of the growth of vascular endothelial cells or angiogenesis as well as for treatment of diseases associated with vascular pathological conditions.

The specification provides the functional limitation of a peptide of the Invention as having at least one activity selected from vascular endothelial cell growth activity, activity in promoting transcription from c-fos promoter, activity in promoting transcription from VEGF promoter and angiogenesis activity (p. 10, lines 15-20). The structural limitations were presented supra and, as detailed there, there is no adequate written description of the peptide claimed beyond the SEQ ID NO: 2 or SEQ ID NO: 1. The specification does not teach any variant, fragment, or derivative of the peptide other than the full-length of SEQ ID NO: 2 or the encoding polynucleotide of SEQ ID NO: 1. The specification also does not teach functional or structural characteristics of the peptide variants and fragments.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, *Genome*

Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

The working examples provided include only the peptide of SEQ ID NO: 2 and there is nothing in the specification that would indicate that a variant, fragment or derivative of this peptide could be used in the procedures in which the peptide of SEQ ID NO: 2 was used. The unpredictability of the art is *very high* with regards to undisclosed variants of the peptide that would be able to have the effects claimed. It would also necessitate a great amount of experimentation and functional testing, both in vitro and in vivo, first to obtain the fragments and variants of the peptide of SEQ ID NO: 2.

Due to the large quantity of experimentation necessary to generate the undisclosed number of derivatives recited in the claims and possibly screen the same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 18-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Bandman O. (US 2002/0137081).

Bandman teaches a plurality of cDNAs or their complements, SEQ ID NOs: 1-850 which may be used on a substrate to diagnose, to stage, to treat or to monitor the progression or treatment of a vascular disorder. The 93 nucleotide sequence of SEQ ID NO: 1 of the instant Application is 100% identical with the polynucleotides 2676-2768 of sequence # 637 of Bandman, which constitute an open reading frame which may be translated in a protein having the same sequence as the peptide of SEQ ID NO: 2 of the instant Application. These cDNAs represent known and novel genes differentially expressed in vascular endothelial cells. each cDNA having SEQ ID NOs: 438-760 is upregulated at least 2.5-fold in activated vascular endothelial tissue ([0053]). The full length cDNAs or fragment thereof may be used to produce purified proteins using recombinant DNA technologies ([0078]). The proteins may contain amino acid substitutions, deletions or insertions made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved ([0079]). Any of the proteins may be administered as pharmaceutical compositions or in combination with other appropriate therapeutic agents, as

therapeutics for atherosclerosis, coronary artery disease, and cerebral stroke ([0113]-[0114])). Thus, even though Bandman does not teach the protein of SEQ ID NO: 2 of the instant Application, their SEQ ID NO: 637 contains an open reading frame that could be used for encoding a peptide within the metes and bounds of the claims, as it would comprise that protein.

Therefore, Bandman et al. anticipate claims 18-26 of the instant Application.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

- Nakao et al. (J Immunol., 164, 2565-2574, 2000) teaches a novel human tumor antigen protein (SART-2) recognized by T cells by combining with major histocompatibility complex (MHC) class I antigens. The cDNA includes an open reading frame (ORF) between nucleotides 2608-2700 which is identical with the polynucleotide sequence of SEQ ID NO: 1 of the instant Application.
- Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNAs. See pages 8-13.
- Baird et al. teach novel forms of human VEGF-A proteins. The preferred use of the VEGF proteins and nucleic acid molecule compositions of the invention is to use such compositions to treat the cardiovascular system and its diseases through effects on anatomy, conduit function, and permeability. Such proteins

and compositions may be used to aid in the treatment of patients with heart disease, wounds, or other ischemic conditions by stimulating angiogenesis in such patients (col. 5, lines 35-48).

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 8:30-17:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

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USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lorraine Spector/ Ph.D.

Primary Examiner, Art Unit 1647